SOME MODERN METHODS OF ORGANIC SYNTHESIS

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1 Formation of carbon–carbon single bonds

In spite of the fundamental importance in organic synthesis of the formation of carbon–carbon single bonds there are comparatively few general methods available for effecting this process, and fewer still which proceed in good yield under mild conditions. Many of the most useful procedures involve carbanions, themselves derived from organometallic compounds, or from compounds containing 'activated' methyl or methylene groups. They include reactions which proceed by attack of the carbanion on a carbonyl or conjugated carbonyl group, as in the Grignard reaction, the aldol and Claisen ester condensations and the Michael reaction, and reactions which involve nucleophilic displacement at a saturated carbon atom, as in the alkylation of ketones and the coupling reactions of some organometallic compounds. Other reactions employed in the formation of carbon–carbon bonds involve carbonium ions and pericyclic processes and recently free-radial reactions have been finding useful application. Examples of all of these procedures will be discussed in this chapter.

1.1. Alkylation: importance of enolate anions

It is well known that certain unsaturated groups attached to a saturated carbon atom render hydrogen atoms attached to that carbon relatively acidic, so that the compound can be converted into an anion on treatment with an appropriate base. Table 1.1, taken from House (1965), shows the pK_a values for some compounds of this type and for some common solvents and reagents.

The acidity of the C—H bonds in these compounds is due to a combinaion of the inductive electron-withdrawing effect of the unsaturated groups and resonance stabilisation of the anion formed by removal of a proton (1.1). Not all groups are equally effective in 'activating' a neighbouring CH_2 or CH_3; nitro is the most powerful of the common groups and thereafter the series follows the approximate order $NO_2 > COR > SO_2R > CO_2R > CN > C_6H_5$. Two activating groups reinforce

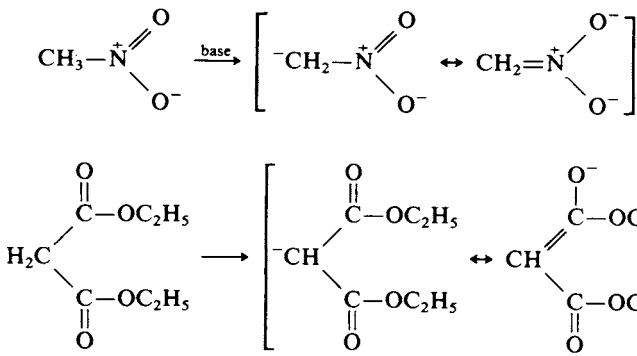
Table 1.1. *Approximate acidities of active methylene compounds and other common reagents*

Compound	pK_a	Compound	pK_a
$CH_3CO_2\underline{H}$	5	$C_6H_5COC\underline{H}_3$	19
$C\underline{H}_2(CN)CO_2C_2H_5$	9	$CH_3COC\underline{H}_3$	20
$C\underline{H}_2(CO.CH_3)_2$	9	$C\underline{H}_3SO_2C\underline{H}_3$	~23
$C\underline{H}_3NO_2$	10	$C\underline{H}_3CO_2C_2H_5$	~24
$CH_3COC\underline{H}_2CO_2C_2H_5$	11	CH_3CO_2H	~24
$C\underline{H}_2(CO_2C_2H_5)_2$	13	$C\underline{H}_3CN$	~25
$CH_3O\underline{H}$	16	$C_6H_5NH_2$	~30
$C_2H_5O\underline{H}$	18	$(C_6H_5)_3C\underline{H}$	~40
$(CH_3)_3CO\underline{H}$	19	$C\underline{H}_3SOC\underline{H}_3$	~40

(Acidic hydrogen atoms are underlined)

H. O. House, *Modern synthetic reactions*, copright 1972, W. A. Benjamin, Inc. Menlo Park, California.

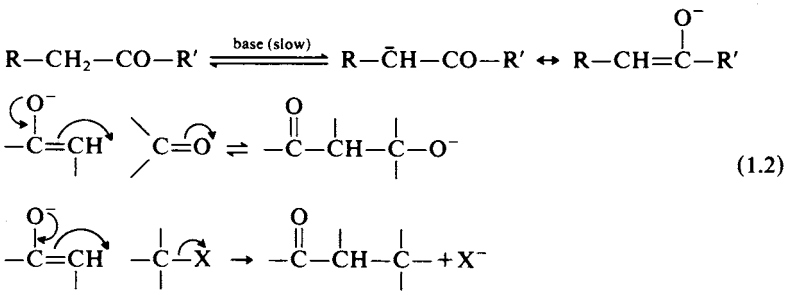
each other, as can be seen by comparing diethyl malonate ($pK_a \approx 13$) with ethyl acetate ($pK_a \approx 24$). Acidity is also increased slightly by electron-withdrawing substituents (e.g. sulphide), and decreased by alkyl groups, so that diethyl methylmalonate, for example, has a slightly less acidic C—H group than diethyl malonate itself.



(1.1)

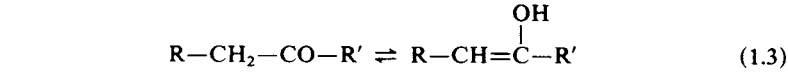
By far the most important activating groups in synthesis are the carbonyl and carboxylic ester groups. Removal of a proton from the α-carbon atom of a carbonyl compound with base gives the corresponding enolate anion, and it is these anions which are involved in base-catalysed condensation reactions of carbonyl compounds, such as the aldol condensation, and in bimolecular nucleophilic displacements (alkylations) (1.2).

The enolate anions should be distinguished from the enols themselves, which are always present in equilibrium with the carbonyl compound. Most monoketones and esters contain only small amounts of enol (< 1



(1.2)

per cent) at equilibrium, but with 1,2- and 1,3-dicarbonyl compounds much higher amounts of enol (>50 per cent) may be present. In the presence of acid catalysts monoketones may be converted largely into the enol form, and enols are concerned in many acid-catalysed condensations of carbonyl compounds (1.3).



(1.3)

The formation of the enolate anion results from an equilibrium reaction between the carbonyl compound and the base. A competing equilibrium involves the enolate anion and the solvent. Thus, with diethyl malonate in solvent SolH in presence of base B^-, we have

$$\begin{aligned} CH_2(CO_2C_2H_5)_2 + B^- &\rightleftharpoons {}^-CH(CO_2C_2H_5)_2 + BH \\ {}^-CH(CO_2C_2H_5)_2 + SolH &\rightleftharpoons CH_2^{\cdot}(CO_2C_2H_5)_2 + Sol^-, \end{aligned} \tag{1.4}$$

and to ensure an adequate concentration of the enolate anion at equilibrium clearly both the solvent and the conjugate acid of the base must be much weaker acids than the active methylene compound. The correct choice of base and solvent is thus of great importance if the subsequent alkylation, or other, reaction is to be successful. Reactions must normally be effected under anhydrous conditions since water is a much stronger acid than the usual activated methylene compounds and, if present, would instantly protonate any carbanion produced. Another point of importance is that the solvent must not be a much stronger acid than the conjugate acid of the base, otherwise the equilibrium

$$B^- + SolH \rightleftharpoons BH + Sol^- \tag{1.5}$$

will lie too far to the right and lower the concentration of B^-. For example,

sodamide can be used as base in liquid ammonia or in benzene, but, obviously, not in ethanol. Base-solvent combinations commonly used to convert active methylene compounds into the corresponding anions include sodium methoxide, sodium ethoxide and sodium or potassium t-butoxide in solution in the corresponding alcohol, or as suspensions in ether, benzene or dimethoxyethane. Potassium t-butoxide is a particularly useful reagent, since it is a poor nucleophile and its solutions in different solvents have widely different basic strengths; it is most active in solution in dry dimethyl sulphoxide (Pearson and Buehler, 1974). Metallic sodium or potassium, or sodium hydride, in suspension in benzene, ether or dimethoxyethane, sodamide in suspension in an inert solvent or in solution in liquid ammonia, and solutions of sodium or potassium triphenylmethyl in ether or benzene have also been used with the less 'active' compounds.

For many purposes, however, these traditional bases have now been superseded by the lithium salts of certain sterically hindered secondary amines, particularly lithium diisopropylamide and lithium 2,2,6,6-tetramethylpiperidide (Olofson and Dougherty, 1973) or the alkali metal salts of bis(trimethylsilyl)amine, $HN(SiMe_3)_2$ (Colvin, 1978; Smith and Richmond, 1983). These strong amide bases are only weakly nucleophilic, so that they do not themselves attack susceptible functional groups, and they have the added advantage that they are soluble in non-polar, even hydrocarbon, solvents. The insolubility of the traditional bases in most common organic solvents seriously limits their usefulness.

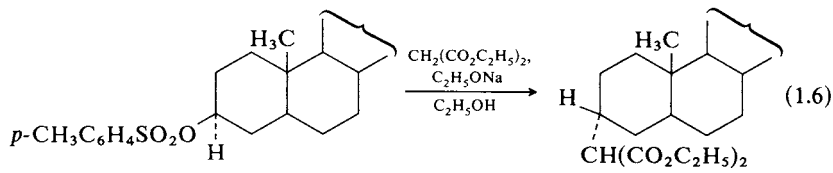
1.2. Alkylation of relatively acidic methylene groups

In order to effect a reasonably rapid reaction it is, of course, necessary to have a high concentration of the appropriate carbanion. Because of their relatively high acidity (see Table 1.1) compounds in which a C—H bond is activated by a nitro group or by two or more carbonyl, ester or cyano groups can be converted largely into their anions with a comparatively weak base such as a solution of sodium ethoxide in ethanol. An alternative procedure is to prepare the enolate in benzene or ether, using finely divided sodium or potassium metal or sodium hydride, which react irreversibly with compounds containing active methylene groups with formation of the metal salt and evolution of hydrogen. β-Diketones can often be converted into their enolates with alkali metal hydroxides or carbonates in aqueous alcohol or acetone.

Much faster alkylation of enolate anions can often be achieved in dimethylformamide, dimethyl sulphoxide, 1,2-dimethoxyethane or hexamethylphosphoramide than in the usual protic solvents. This appears to be due to the fact that the former solvents do not solvate the enolate

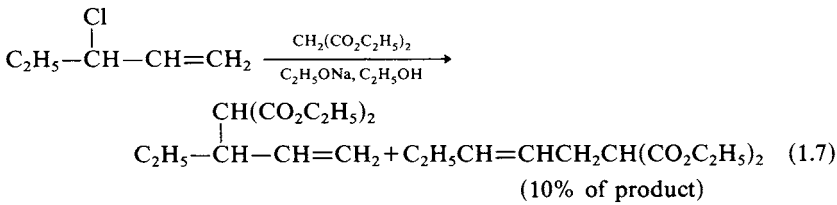
anion and thus do not diminish its reactivity as a nucleophile. At the same time they are able to solvate the cation, separating it from the cation–enolate ion pair and leaving a relatively free enolate ion which would be expected to be a more reactive nucleophile than the ion pair (Parker, 1962). Reactions effected with aqueous alkali as base are often improved in the presence of a phase-transfer catalyst such as a tetraalkylammonium salt (cf. Makosza and Jończyk, 1976).

Alkylation of enolate anions is readily effected with alkyl halides or other alkylating agents. Both primary and secondary alkyl, allyl or benzyl halides may be used successfully, but with tertiary halides poor yields of alkylated product often result because of competing dehydrohalogenation of the halide. It is often advantageous to proceed by way of the toluene-*p*-sulphonate or methanesulphonate rather than a halide. The sulphonates are excellent alkylating agents, and can usually be obtained from the alcohol in a pure condition more readily than the corresponding halides. Epoxides have also been used as alkylating agents, generally reacting at the less substituted carbon atom. Attack of the enolate anion on the alkylating agent takes place by an S_N2 pathway and thus results in inversion of configuration at the carbon atom of the alkylating agent.



(1.6)

With secondary and tertiary allylic halides or sulphonates, reaction of an enolate anion may give mixtures of products formed by competing attack at the α- and γ-positions (1.7).



(1.7)

A difficulty sometimes encountered in the alkylation of active methylene compounds is the formation of unwanted dialkylated products. During the alkylation of diethyl sodiomalonate, the monoalkyl derivative formed initially is in equilibrium with its anion as indicated in the first equation of (1.8). In ethanol solution, dialkylation does not take place to any appreciable extent because ethanol is sufficiently acidic to reduce

the concentration of the anion of the alkyl derivative, but not that of the more acidic diethyl malonate itself, to a very low value.

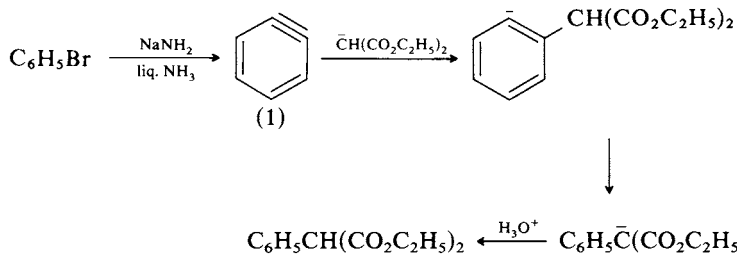
$$\begin{aligned} RCH(CO_2C_2H_5)_2 + \bar{C}H(CO_2C_2H_5)_2 &\rightleftharpoons R\bar{C}(CO_2C_2H_5)_2 + CH_2(CO_2C_2H_5)_2 \\ R\bar{C}(CO_2C_2H_5)_2 + C_2H_5OH &\rightleftharpoons RCH(CO_2C_2H_5)_2 + C_2H_5O^- \end{aligned} \qquad (1.8)$$

However, replacement of ethanol by an inert solvent favours dialkylation, and dialkylation also becomes a more serious problem with the more acidic alkylcyanoacetic esters, and in alkylations with very reactive compounds such as allyl or benzyl halides or sulphonates.

Dialkylation may, of course, be effected deliberately if required by carrying out two successive operations, using either the same or a different alkylating agent in the two steps. Thus, alkylation with $\alpha\omega$-polymethylene dihalides, and intramolecular alkylation of ω-haloalkylmalonic esters provides a useful route to three- to seven-membered ring compounds. Non-cyclic products are frequently formed at the same time by competing intermolecular reactions and conditions have to be carefully chosen to suppress their formation (1.9).

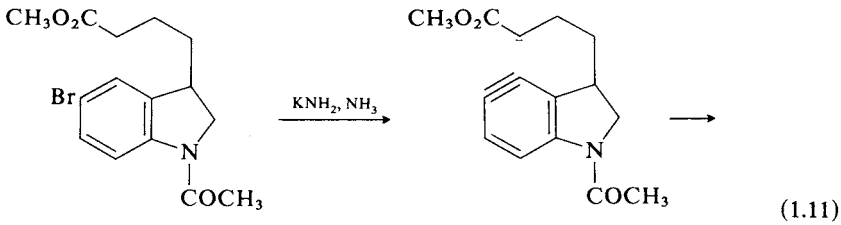
$$Br(CH_2)_3Br + CH_2(CO_2C_2H_5)_2 \xrightarrow[C_2H_5OH]{NaOC_2H_5} \begin{array}{l} \text{cyclopropane-1,1-dicarboxylate} \\ + \text{cyclopentane-1,1-bis(malonate)} \end{array} \qquad (1.9)$$

Under ordinary conditions aryl or vinyl halides do not react with enolate anions, although aryl halides with strongly electronegative substituents in the *ortho* and *para* positions do. 2,4-Dinitrochlorobenzene, for example, with ethyl cyanoacetate gives ethyl (2,4-dinitrophenyl)cyanoacetate in 90 per cent yield by an addition–elimination, not an S_N2, pathway. Unactivated aryl halides may also react with enolates under more vigorous conditions. Reaction of bromobenzene with diethyl malonate, for example, takes place readily in presence of an excess of sodium amide in liquid ammonia, to give diethyl phenylmalonate in 50 per cent yield. The reaction is not a direct nucleophilic displacement, however, but takes place by an elimination–addition sequence in which benzyne is an intermediate (1.10). Similar reactions can be effected intramolecularly and provide a good route to some cyclic systems (1.11). Vinyl derivatives of active methylene compounds can be obtained indirectly from alkylidene derivatives by moving the double bond out of conjugation as illustrated in (1.12). Kinetically controlled alkylation of the delocalised anion takes place at the α-carbon atom to give the

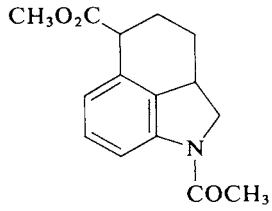


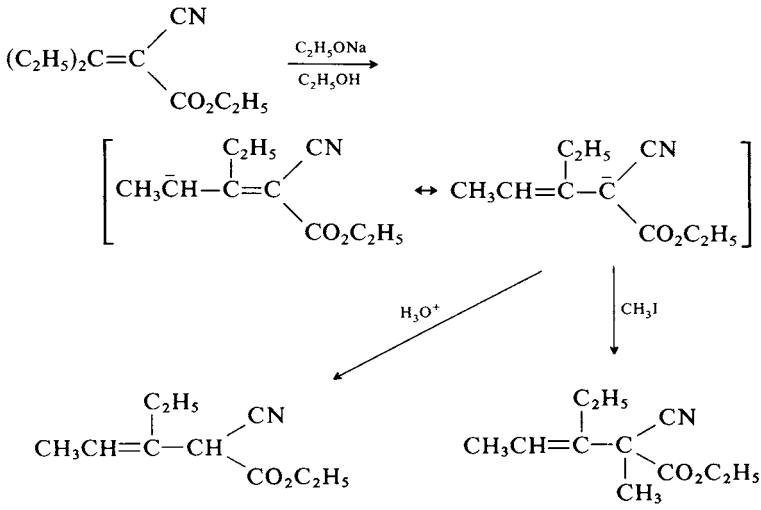
(1.10)

$\beta\gamma$-unsaturated compound directly. A similar course is followed in the kinetically controlled protonation of such anions.



(1.11)





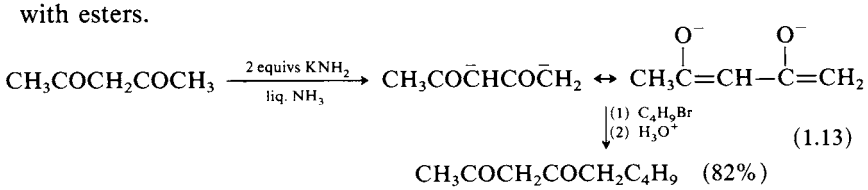
(1.12)

A wasteful side reaction which frequently occurs in the alkylation of 1,3-dicarbonyl compounds is the formation of the *O*-alkylated product. Thus, reaction of the sodium salt of cyclohexan-1,3-dione with butyl bromide gives 37 per cent of 1-butoxycyclohexen-3-one and only 15 per cent of 2-butylcyclohexan-1,3-dione. In general, however, *O*-alkylation competes significantly with *C*-alkylation only with reactive methylene compounds in which the equilibrium concentration of enol is relatively high, as in 1,3-dicarbonyl compounds and phenols. Phenols, of course, generally undergo predominant *O*-alkylation.

Alkylation of malonic ester, cyanacetic ester and β-keto esters is useful in synthesis because the alkylated products on hydrolysis and decarboxylation or, better, by direct decarbalkoxylation under neutral conditions with an alkali metal salt (for example, lithium chloride) in a dipolar aprotic solvent such as dimethylformamide (Krapcho, 1982) afford carboxylic acids (esters) or ketones. From alkylated malonic or cyanoacetic esters, substituted acetic acids or esters are obtained, and alkylated acetoacetic esters give methyl ketones.

1.3 γ-Alkylation of 1,3-dicarbonyl compounds; dianions in synthesis

Alkylation of a 1,3-diketone or a β-keto-ester at a 'flanking' methyl or methylene group instead of at the doubly activated methylene or methine does not usually take place to any significant extent under 'ordinary' conditions. It can be accomplished selectively and in good yield, however, by way of the corresponding *dianion*, itself prepared from the diketone and two equivalents of a suitable strong base such as sodamide or lithium diisopropylamide, by reaction with one equivalent of alkylating agent (Harris and Harris, 1969). Thus, 2,4-pentanedione is converted into 2,4-nonanedione in 82 per cent yield (1.13) by reaction at the more reactive less resonance-stabilised carbanion and 1,6-diphenyl-1,3-pentanedione is obtained in 77 per cent yield by reaction of the dianion of benzylacetone with benzyl chloride. Keto acids and triketones can also be obtained by reaction of the dianions with carbon dioxide or with esters.

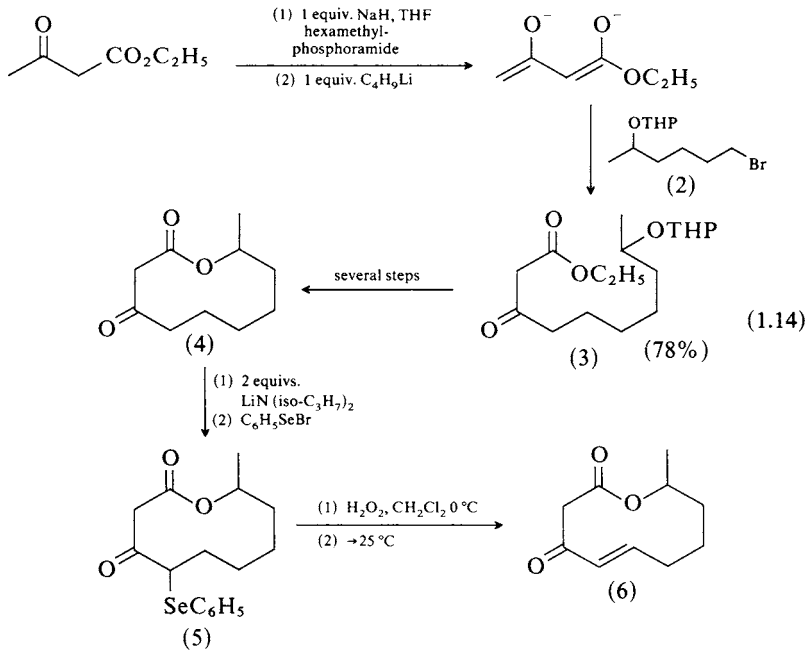


(1.13)

With unsymmetrical diketones which could apparently give rise to two different dianions, it is found in practice that in most cases only one is formed, and a single product results on alkylation. Thus, with 2,4-

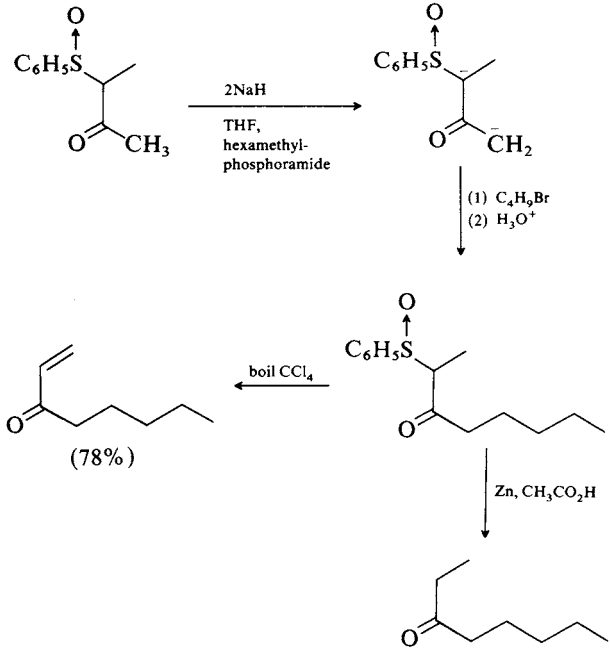
hexanedione alkylation at the methyl group greatly predominates over that at the methylene group, and 2-acetylcyclohexanone and 2-acetylcyclopentanone are both alkylated exclusively at the methyl group. In general, the ease of alkylation follows the order $C_6H_5CH_2 > CH_3 > CH_2$.

The reaction can be applied equally well to β-keto aldehydes and β-keto esters, and, in the latter case, provides a useful route to 'mixed' Claisen ester condensation products. Reactions with β-keto aldehydes are generally effected by treating the prepared monosodium salt of the aldehyde with alkali amide, to prevent self-condensation of the aldehyde. With β-keto esters the dianions are conveniently prepared by reaction with two equivalents of lithium diisopropylamide, and give γ-alkylated products in high yield with a wide range of alkylating agents (Huckin and Weiler, 1974). The dianion generated in this way from ethyl acetoacetate, for example, has been used in the synthesis of a number of natural products. An example is seen in the synthesis of the ten-membered lactone (±)-diplodialide A (6) where, in fact, the reaction is used twice; once to prepare the β-keto-ester (3) by alkylation of the dianion of ethyl acetoacetate with the bromide (2), and again to introduce the double bond of diplodialide A by reaction of the dianion of the β-keto lactone (4) with phenylselenyl bromide to give the γ-phenylselenide (5). Elimination by way of the derived selenoxide (cf. p. 121) then led to diplodialide A (Ishida and Wada, 1979).



(1.14)

Dianions are now being widely employed in synthesis and their application is not confined to γ-alkylation of β-dicarbonyl compounds. Dianions derived from β-keto sulphoxides are alkylated at the γ-carbon atom, and the auxiliary sulphoxide group can subsequently be removed after alkylation by pyrolysis or reductive-cleavage to give $\alpha\beta$-unsaturated or α-alkylated ketones (Grieco and Pogonowski, 1974) (1.15).



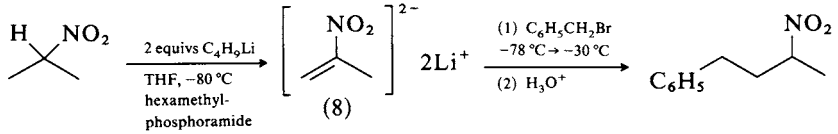
(1.15)

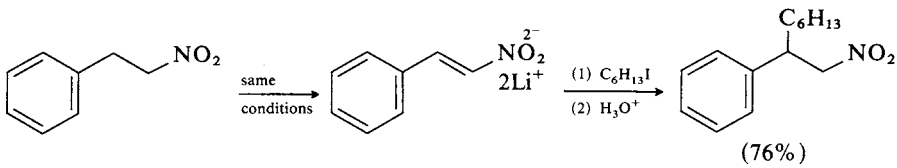
Synthetically useful results have been obtained recently with dianions derived from nitroalkanes. Primary nitro-alkanes, RCH_2NO_2, can be deprotonated twice in the α-position to give dianions (7) which, in contrast to simple nitronates (the *mono*anions) give *C*-alkylated products in good yield. With the monoanions alkylation takes place mainly on oxygen (Seebach *et al.*, 1977).

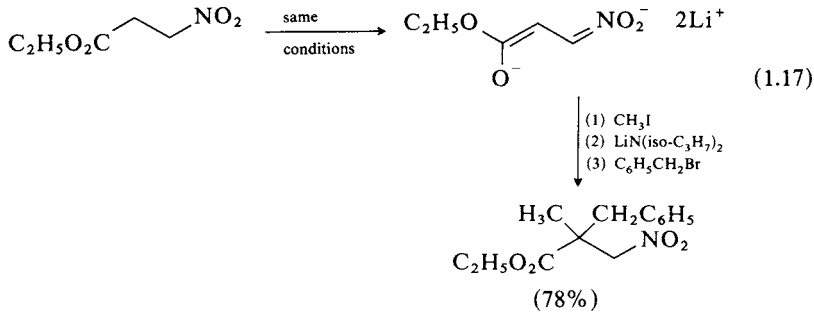
$$C_2H_5CH_2NO_2 \xrightarrow{2\text{ equivs } C_4H_9Li} \underset{(7)}{C_2H_5\bar{C}{=}NO_2^-2Li^+} \xrightarrow[(2)\ H_3O^+]{(1)\ C_6H_5CH_2Br} C_2H_5\underset{\displaystyle CH_2C_6H_5}{\underset{|}{C}}HNO_2 \quad (53\%) \qquad (1.16)$$

If there is only one α-hydrogen atom, as in 2-nitropropane, the $\alpha\beta$-doubly

deprotonated species (8) is formed and on alkylation affords the β-alkyl derivative, again by reaction at the less stabilised carbanion. The same is true when another activating group such as an aryl group or a carbethoxy group is present in the β-position. Ethyl β-nitropropionate, for example, by reaction with two equivalents of butyl-lithium, forms a dianion which is readily alkylated with primary or secondary alkyl halides at the position α to the ester group.



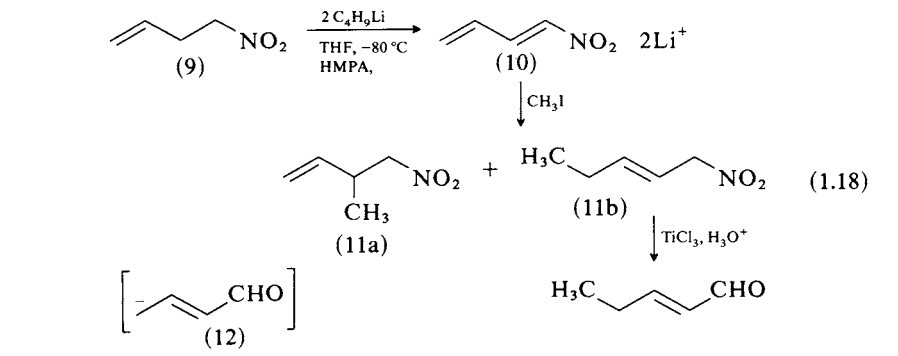




(1.17)

Similarly the γδ-unsaturated nitro compound (9) undergoes double deprotonation to give a dark red solution of the αβ-dianion (10). With electrophiles, for example methyl iodide, this gives mainly the δ-substitution product (11*b*). This can be converted into an αβ-unsaturated aldehyde by reduction of the nitro group with Ti(III) chloride. In this sequence the nitro compound (9) is synthetically equivalent to the crotonaldehyde anion (12) (Seebach, Henning and Lehr, 1978).

In a different kind of application, β-hydroxy carboxylic esters have been converted stereoselectively into α-alkyl derivatives without protection of the hydroxyl group (1.19) (Fráter, 1979).



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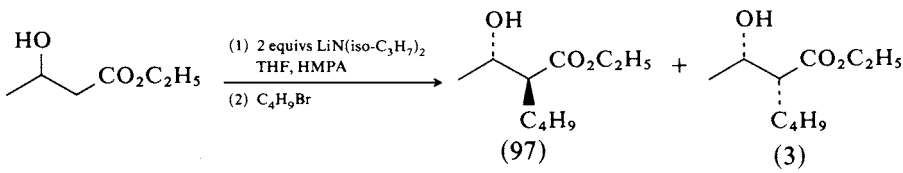
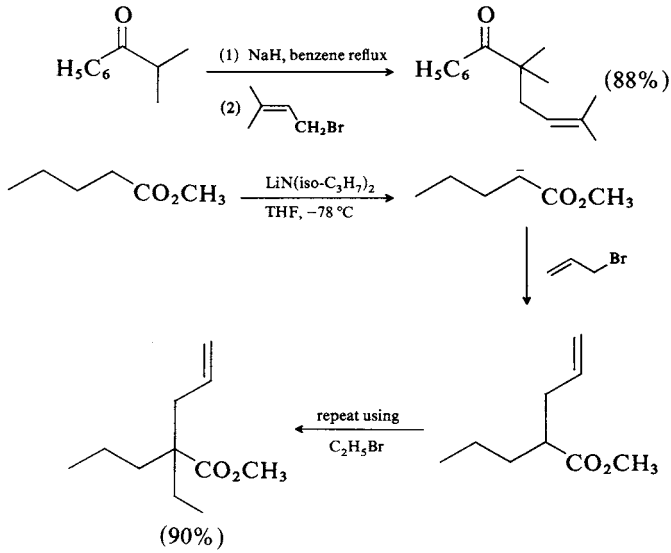


(1.19)

1.4. Alkylation of ketones

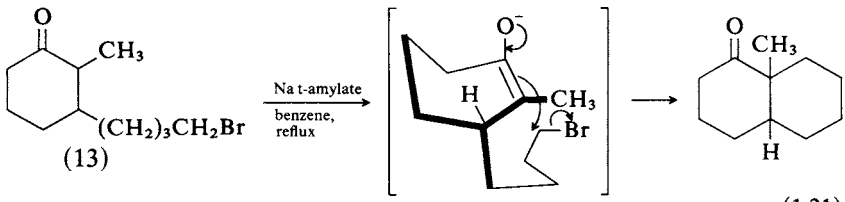
Alkylation of monofunctional carbonyl compounds, aldehydes, ketones and esters, is more difficult than that of the 1,3-dicarbonyl compounds discussed above. As can be seen from Table 1.1, a methyl or methylene group which is activated by only one carbonyl, ester or cyano group requires a stronger base than sodium ethoxide or methoxide to convert it into the enolate anion in high enough concentration to be useful for subsequent alkylation. Alkali metal salts of tertiary alcohols, such as t-butanol or t-amyl alcohol, in solution or suspension in the corresponding alcohol or in an inert solvent, have been used with success, but suffer from the disadvantage that they are not sufficiently basic to convert the ketone completely into the enolate anion, thus allowing the possibility of an aldol condensation between the anion and unchanged carbonyl compound. An alternative procedure is to use a much stronger base which will convert the compound completely into the anion. Typical bases of this type are sodium and potassium amide, sodium hydride, and sodium and potassium triphenylmethyl, in such solvents as ether, benzene, dimethoxyethane or dimethylformamide. The alkali metal amides are often used in solution in liquid ammonia. Although these bases can convert ketones essentially quantitatively into their enolate anions, aldol condensation may again be a difficulty with sodium hydride or sodamide in inert solvents, because of the insolubility of the reagents. Formation of the anion takes place only slowly in the heterogeneous reaction medium and both the ketone and the enolate ion are present at

some point. This difficulty does not arise with the lithium dialkylamides, such as lithium diisopropylamide or lithium 2,2,6,6-tetramethylpiperidide or the alkali metal salts of bis(trimethylsilyl)amine (p. 4), which are soluble in non-polar solvents, and these bases have now largely replaced the more traditional reagents for the generation of enolate anions.



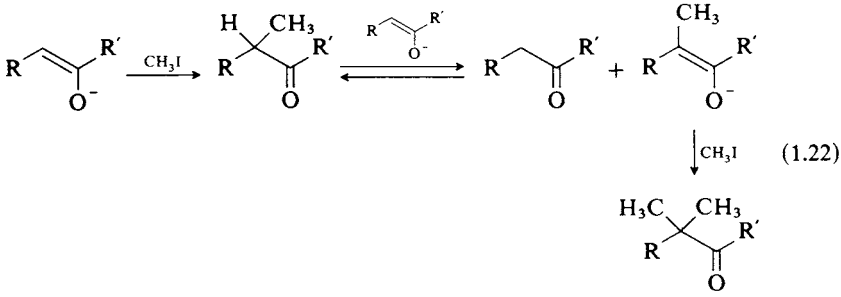
(1.20)

Examples illustrating the base-catalysed intermolecular alkylation of a ketone and an ester are given in (1.20). Intramolecular alkylations also take place readily in appropriate cases, and reactions of this kind have been widely used in the synthesis of cyclic compounds. *Cis*-9-methyl-1-decalone, for example, is smoothly obtained from the ketone (13) in presence of sodium t-amylate(pentanoate). In these alkylation reactions the alkylating agent generally approaches the enolate from the less hindered side and in a direction orthogonal to the plane of the enolate anion.



(1.21)

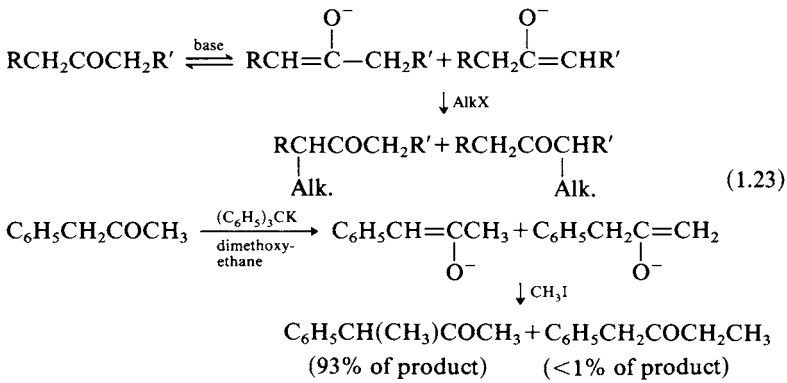
A common side reaction in the direct alkylation of ketones is the formation of di- and poly-alkylated products through interaction of the original enolate with the monoalkylated compound (1.22).



(1.22)

This difficulty can be avoided to some extent by adding a solution of the enolate in a polar co-ordinating solvent such as dimethoxyethane to a large excess of the alkylating agent. The enolate may therefore be rapidly consumed before equilibration with the alkylated ketone can take place. Nevertheless, formation of polysubstituted products is a serious problem in the direct alkylation of ketones and often results in decreased yields of the desired monoalkyl compound.

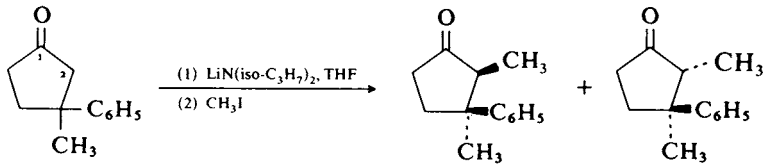
Alkylation of symmetrical ketones and of ketones which can enolise in one direction only can, of course, give only one mono-*C*-alkylated product. With unsymmetrical ketones, however, two different monoalkylated products may be formed by way of the two structurally isomeric enolates (1.23). But if one of the isomeric enolate anions is stabilised by conjugation with another group such as cyano, nitro or ethoxycarbonyl, then for all practical purposes only this stabilised anion is formed and alkylation takes place at the position activated by both groups. Even an α-phenyl or a conjugated carbon–carbon double bond provides sufficient stabilisation of the resulting anion to direct substitution into the adjacent position (1.23).



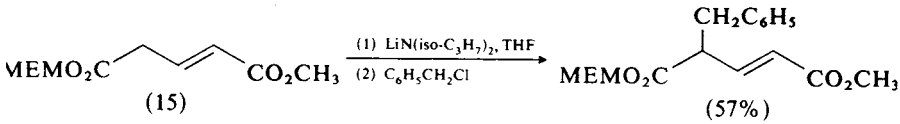
(1.23)

Sometimes, specific lithium enolates of unsymmetrical carbonyl compounds are formed because of chelation of the lithium with some suitably

placed substituent. Thus, reaction of the cyclopentanone (14) with lithium diisopropylamide followed by alkylation gave largely the product formed by alkylation at the more hindered α-position, adjacent to the phenyl substituent. This is believed to be due to preferential formation of the C-2 lithio enolate because of chelation of the lithium atom in the enolate with the phenyl substituent (Posner and Lenz, 1979). Again, lithiation of the mixed ester (15) took place α to the MEM ester group, presumably as a result of intramolecular chelation of lithium with the ethereal oxygen (Cox, Heaton and Horbury, 1980).



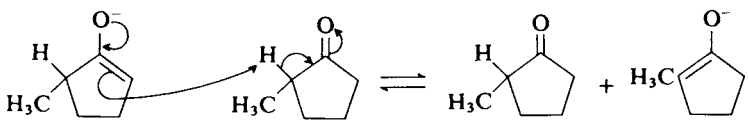
(14) (1.24)



(15) (57%)

MEM=$CH_3OCH_2OCH_2$

Alkylation of unsymmetrical ketones bearing only α-alkyl substituents, however, generally leads to mixtures containing both α-alkylated products. The relative amounts of the two products depend on the structure of the ketone and may also be influenced by experimental factors such as the nature of the cation and the solvent (see Table 1.2). In the presence of the free ketone or of another proton source such as a protic solvent, equilibration of the two enolate ions can take place. Therefore if the enolate is prepared by slow addition of the base to the ketone, or if an excess of the ketone remains after the addition of base is complete, the equilibrium mixture of enolate anions is obtained containing preponderantly the more substituted enolate. Slow addition of the ketone to an



(1.25)

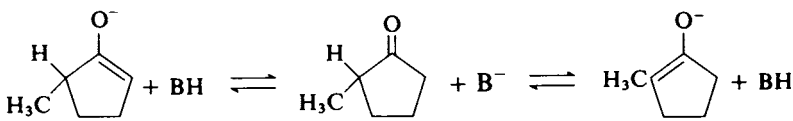
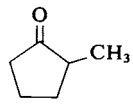
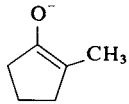
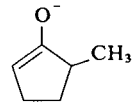
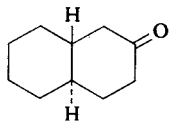
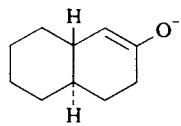
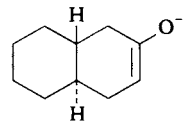


TABLE 1.2 *Composition of mixtures of enolate anions generated from the ketone and a triphenylmethyl metal derivative in dimethoxyethane*

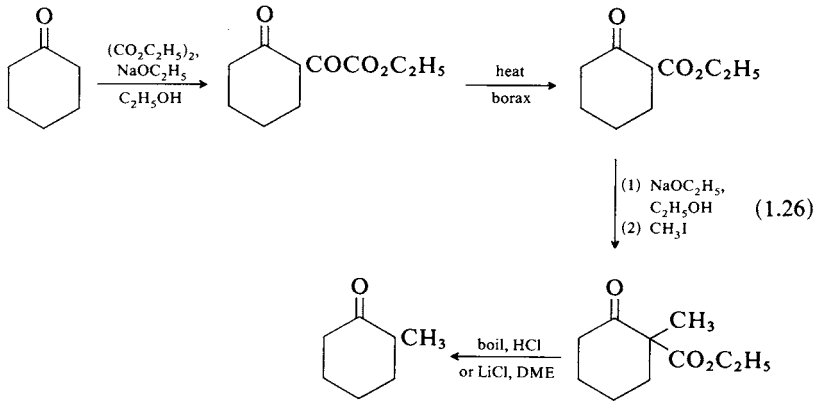
(House, 1967)

Ketone, cation and reaction conditions	Enolate anion composition %	
		
K^+ (kinetic control)	55	45
K^+ (equil. control)	78	22
Li^+ (kinetic control)	28	72
Li^+ (equil. control)	94	6
		
Li^+ (kinetic control)	13	87
Li^+ (equil. control)	53	47
$C_4H_9CH_2COCH_3$	$C_4H_9CH{=}C(O^-){-}CH_3$	$C_4H_9CH_2C(O^-){=}CH_2$
K^+ (kinetic control)	46	54
K^+ (equil. control)	58	42
Li^+ (kinetic control)	30	70
Li^+ (equil. control)	87	13

excess of a strong base in an aprotic solvent, on the other hand, leads to the kinetic mixture of enolates; under these conditions the ketone is completely converted into the anion and equilibration does not occur.

The composition of mixtures of enolates formed under kinetic conditions differs from that of mixtures formed under equilibrium conditions. In general, enolate mixtures formed under kinetic conditions contain more of the less highly substitued enolate than the equilibrium mixture, reflecting the fact that the less hindered α-protons are removed more rapidly by the base. However, whichever method is used, mixtures of both structurally isomeric enolates are generally obtained, and mixtures of products result on alkylation. Di- and tri-alkylation products may also be formed (see p. 13) and it is not always easy to isolate the pure monoalkylated compound from the resulting complex mixtures. This is a serious problem in synthesis since in many cases it results in the loss of valuable starting materials.

A number of methods have been used to improve selectivity in the alkylation of unsymmetrical ketones and to reduce the amount of polyalkylation. One widely used procedure is to introduce temporarily an activating group at one of the α-positions to stabilise the corresponding enolate anion; this group is removed later after the alkylation has been effected. Common activating groups used for this purpose are the ethoxycarbonyl, ethoxyoxalyl and formyl groups. Thus, to prepare 2-methylcyclohexanone from cyclohexanone the best procedure is to go through the 2-ethoxycarbonyl derivative, which is easily obtained from the ketone by reaction with ethyl carbonate, or by condensation with diethyl oxalate followed by decarbonylation. Conversion into the enolate ion with a base such as sodium ethoxide takes place exclusively at the doubly activated position. Methylation with methyl iodide, and removal of the β-ketoester group with acid or base gives 2-methylcyclohexanone, free from polyalkylated products.



(1.26)

Another technique is to block one of the α-positions by introduction of a removable substituent which *prevents* formation of the corresponding enolate. A widely used method is acylation with ethyl formate and transformation of the resulting formyl or hydroxymethylene substituent into a group that is stable to base, such as an enamine, an enol ether or an enol thioether. An example of this procedure is shown below in the preparation of 9-methyl-1-decalone from *trans*-1-decalone. Direct alkylation of this compound gives mainly the 2-alkyl derivative (1.27). A useful alternative procedure is alkylation of the dianion prepared from the formyl derivative with potassium amide (p. 9).

Specific enolate anions may also be obtained from unsymmetrical ketones by way of the structurally specific enol acetates or, better, the trimethylsilyl enol ethers. Reaction of the latter with one equivalent of methyl-lithium in dimethoxyethane affords the corresponding lithium